TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
FLAMEL0088		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2004/050603	19.11.2004	21.11.2003

International Patent Classification (IPC) or national classification and IPC

A61K38/21, A61K9/14, A61K38/20, A61K47/42

Applicant

FLAMEL TECHNOLOGIES

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:

      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FR2004/050603

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-8, 10-15, 17-31 as originally filed/furnished

pages* 9,16 received by this Authority on 24.09.2005 with letter of 21.09.2005

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1,2,3(in part), 7(in part), 8, 13-34 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 3(in part),4-6, 7(in part), 9-12 received by this Authority on 24.09.2005 with letter of 21.09.2005

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/2, 2/2 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	10-11	YES
	Claims	1-9, 12-34	NO
Inventive step (IS)	Claims		YES
	Claims	1-34	NO
Industrial applicability (IA)	Claims	1-34	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: FR-A-2 786 098
D2: FR-A-2 732 218
D3: FR-A-2 801 226
D4: FR-A-2 822 834
D5: FR-A-2 838 964
D6: WO 99/18142 A

Unless otherwise indicated, reference is also made to the relevant passages cited in the international search report for the said documents.

2.1

D1 to D6 all describe colloidal suspensions of submicronic particles vectoring active principles (AP), based on polymers that are biodegradable, water soluble and have hydrophobic groups. Said formulations form spontaneously by dispersal in water and enable the sustained release of AP after parenteral administration.

In D1, poly(Glu) or poly(Asp) polymers are used. The duration of *in vivo* release of insulin is however limited to 12 hours in D1, contrary to the formulations of the present application that enable the active principle to be released over more than 24 hours. Hence, claims 1 to 34 appear novel over D1 (PCT Article 33(2)).

In D2-D3, the polymers used contain a first type of monomer

consisting of Glu and/or Asp amino acids and a second type of hydrophobic monomer consisting of Leu, Ile, Ala, Val, Pro and Phe amino acids.
D2 does not disclose a formulation enabling the active principle to be released over more than 24 hours (formulations enabling a system for sustained, controlled release, with no indication of the duration, are specified on pages 8 and 18 of D2). Hence, claims 1 to 34 appear novel over D2 (PCT Article 33(2)).

However, the release of insulin over more than 24 hours, as described in claim 1, is disclosed in D3. Hence, claims 1, 6 to 9, 12 to 16, 21 to 23 and 25 to 34 are not novel over D2–D3 (PCT Article 33(2)).

In D4, the polymers used contain a first type of monomer consisting of Glu and/or Asp amino acids and a second type of hydrophobic monomer consisting of Leu, Ile, Ala, Val, Pro and Phe amino acids. The polymers according to D4 further contain a PEG-type hydrophilic polymer. Moreover, the formulations according to D4 enable *in vivo* release of insulin for more than 30 hours. Hence, claims 1, 6 to 9, 12 to 23 and 25 to 34 are not novel over D4 (PCT Article 33(2)).

The "gelled deposit" is not mentioned in D3–D4. However, the other technical features of the formulations of the present application are the same. It can therefore be deduced that the formation of the gelled deposit is an implicit feature of the prior art formulations (even though it was not mentioned or observed at the time) and that the latter are also "capable" of forming said gel *in vivo*. It is also advisable to add that the feature "capable…of forming a gelled deposit *in vivo*, which on the one hand, is at least partially caused by at least one physiological protein present *in vivo*" does not constitute a technical feature but rather a functional feature (desired effect or property) that is not clear and supported as required by PCT Articles 5 and 6. A definition according to the "desired result" does not enable the scope of the protection sought to be determined. The fact that

each formulation could be tested does not dispel this objection, since, apart from the compounds described in the description, a person skilled in the art does not initially know whether such a formulation comes within the scope of the claim. An excessive number of tests would be necessary to test each formulation randomly. The part "on the one hand, at least partially caused by at least one physiological protein present *in vivo*" is even less clear ("at least partially… by at least one…") and cannot be verified without excessive effort by a person skilled in the art (tests to be carried out *in vivo*). On the contrary, the other features of the formulations described in D3–D4 are the same, as already mentioned above, and even if the formation of the "gelled deposit" is not mentioned in said documents, the technical features whereby the subject matter of the present application can be differentiated from that of the prior art appear neither in the claims nor in the description. The present application therefore appears to provide no novel and inventive technical effect relative to prior art documents D3–D4.

In D5, the polymers used are arrangements of Glu and/or Asp polyamino acids with hydrophobic polymers, preferably lactic acid or glycolic acid polymers. No release of active principle over more than 24 hours is described in D5. Hence, claims 1 to 34 are novel over D5 (PCT Article 33(2)).

In D6, the polymers are triblock polymers that have hydrophobic groups. After injection into the human body, said polymers spontaneously form a gelled deposit, as described in the present application. A colloidal aqueous suspension may first be prepared at low temperature before being injected *in vivo*, where it then forms a gel when the temperature reaches or exceeds the setting temperature. D6 also states that the thermal gelling behaviour is not pH-dependent. According to D6, the controlled release of active principle is possible by adjusting the concentration of the polymer present. Moreover, example 9 of D6 describes the controlled liberation of paclitaxel over 50 days. Hence, claims 1 to 3, 16, 21 to 23 and 25 to 34 are not novel over D6 (PCT Article

33(2)).

None of the prior art documents measures the concentration of the polymer according to the "induced gelling" concentration (CI) and discloses the viscosity of the formulations obtained. However, claims 4 to 5 and 24 are not considered novel given that all the other features of the formulations of claim 1 are identical to those of the prior art (PCT Article 33(2)). The induced gelling concentration and the viscosity must therefore also be the same. Here again, the distinction between the subject matter of the present application and that of the prior art is not clear.

Hence, only claims 10 to 11 appear novel over D1-D6 (PCT Article 33(2)).

2.2

The formulations of claims 10 to 11 do not involve an inventive step, since they correspond to alternatives that do not have unexpected effects or properties relative to those of the prior art (PCT Article 33(3)).
As mentioned above, the technical features whereby the subject matter of the present application may be differentiated from that of the prior art are not clear from either the claims or the description. The present application appears to provide no novel and inventive technical effect relative to the prior art.

2.3 Objections with regard to clarity

Claim 21 is contradictory, in that it cannot be dependent on claims 1 to 20. Indeed, claims 1 to 20 include claims 6 to 15, which describe formulations wherein the polymer PO can only be a polyaminoacid (formed by Asp and/or Glu units), and not a polysaccharide for example, as described in claim 21.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO03/104303 (D7)	18.12.2003	03.06.2003	07.06.2002
WO2004/013206 (D8)	12.02.2004	23.07.2003	30.07.2002

See separate sheet

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of: **Box VI**

D7 describes (Glu and/or Asp) polyaminoacids functionalised by alpha-tocopherol and optionally by a PEG graft, and the use thereof for vectoring active principles. The formulations according to D7 are capable of forming a gelled deposit *in vivo*.

D8 also describes (Glu and/or Asp) polyaminoacids functionalised by hydrophobic groups and used for vectoring active principles. The formulations are capable of forming a gelled deposit *in vivo*.